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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,265	SPRINGER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-27,29,30,73-80,83-89 and 94-130* is/are pending in the application.

4a) Of the above claim(s) *89,94-101 and 104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-27,29,30,73-80,83-88,102,103 and 105-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

The letter of Non-compliant Amendment (37 CFR 1.121) mailed on 7/2/04 was an error. The Amendment submitted on 6/4/04 to the claims does list all the claims and therefore is complete.

1. Applicant's amendment, filed 6/4/04, is acknowledged.

2. Claims 25-27,29-30, 73-80, 83-89, 94-130 are pending.

3. Newly submitted claims 94-101, and 104 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the specific antibodies that specifically binds α1, α2, α10, α11, α6, αD, αE and αX are recognized divergent subject matter.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 94-101, and 104 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 89, 94-101, and 104 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

5. Claims 25-27, 29-30, 73-80, 83-88, 102-103, 105-130 are under examination as they read on an antibody that selectively binds to a modified integrin I-domain in the open conformation of αL.

6. Applicant is advised that should claim 73 be found allowable, claim 109 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). It is noted that base claim 25 which claim 73 depends form recites a recombinant antibody.

7. In view of the amendment filed on 6/04/04, only the following rejections are remained.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 25-27, 29-30, 73-80, 83-88, 102, 103, 105-130 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or an antigen binding

fragment thereof, which specifically binds to a modified integrin I-Domain in the open conformation comprises substitutions E284/E301C or K287C/K294C in an αL subunit but not to a modified integrin I-domain in the closed conformation by the substitutions of K289C/K294C, does not reasonably provide enablement for an antibody or an antigen binding fragment thereof which specifically binds to any "modified integrin-I domain" in the open conformation in claim 25, or binds to an activation specific epitope on any "integrin I-domain" in the open conformation in claim 26, or a recombinant anti-integrin antibody, or an antigen binding fragment thereof, which specifically binds to an "integrin I-domain" in the open conformation in claim 30, wherein said antibody comprises a "portion of a human antibody" and a "portion of a non-human antibody" in claim 76, any antibody or an antigen binding fragment thereof, which binds to an "integrin I-domain" in the open conformation but not to an "integrin I-domain" in the closed conformation in claim 83, which binds to a modified integrin I-domain in the open conformation but not to any modified integrin I-domain in the closed conformation in claim 85, wherein the modified integrin I-domain in open conformation is modified by introduction of a disulfide bond in claim 86, further comprising a therapeutic moiety in claims 117-121, wherein the therapeutic moiety comprises a cytotoxin in claim 122, a radioactive metal ion in claim 123, a chemical therapeutic agent in claim 124, a protein possessing a desired biological activity in claim 125, a toxin in claim 126, a pharmaceutical composition in claims 127-130. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In view of the Dr. Cohen Declaration filed on 6/04/004 under 37 CFR 1 .132 and applicant's arguments regarding the rejections under rejected under 35 U.S.C. 112, first paragraph enablement, the specification provides enablement for an antibody or an antigen binding fragment thereof, which specifically binds to a modified integrin I-Domain in the open conformation comprises substitutions E284/E301C or K287C/K294C in an αL subunit but not to a modified integrin I-domain in the closed conformation by the substitutions of K289C/K294C.

Besides the antibody or an antigen binding fragment thereof, which specifically binds to a modified integrin I-Domain in the open conformation comprises substitutions E284/E301C or K287C/K294C in an αL subunit but not to a modified integrin I-domain in the closed conformation by the substitutions of K289C/K294C, the specification fails to provide sufficient guidance and direction as to make and use antibodies that binds any "modified integrin I-domain in the open conformation", any "activation specific epitope on an integrin I-domain in the open conformation", any "integrin I-domain in the open conformation", any "LFA-1 integrin in the open conformation", any "integrin I-domain in the open conformation but not to an integrin I-domain in the closed conformation", any modified integrin I-domain in the open conformation but not to a modified integrin I-domain in the closed conformation".

Applicant is relying upon a single species to support an entire genus. The claims as written encompass a broad genus of antibodies with an unlimited number of possibilities with regard to the source and type of molecule that contains the I-domain and the conformation status of the I-domain. Dr. Cohen's Declaration provides only one species of an antibody (IgG#57) that binds

to the I-domain in the open conformation (K287C/294C) in the αL subunit, but not to the I-domain in the closed conformation by the substitutions K289C/K294C) in the αL subunit, yet Applicant claims an antibody that binds any I-domain in the open conformation (i.e., any alpha subunit containing I-domain whether it derives from human, mouse, rat, among others). It is noted that the specification on page 67, last paragraph discloses that the monoclonal antibodies BL5, F8.8, CBRLFA-1/9, May.03, TS1/22 and TS2/6 strongly inhibited binding of both wild type and mutant K287C/K294C, and the levels of inhibition to wild type LFA-1 and the mutant were similar. Further the specification discloses that monoclonal antibodies TS1/11 and TS1/12 inhibited >90% binding of transfectants that express wild type LFA1, these antibodies showed reduced inhibition on binding of mutant K287C/D294C (40-60%). Furthermore, Monoclonal antibodies TS2/14, 25-3-1 and CBRLFA-1/1 show >90% inhibition on binding of wild type but had no to little inhibition on mutant K287C/K294C binding to ICAM-1. Finally, Table 3 in the specification at page 69, provides no single example of an antibody that binds the open conformation but not the closed conformation of the LFA-1. In the contrary Table 3, provides antibody that binds either to both closed and opened conformation or to the closed conformation but not to the opened conformation. It is not clear how one of skill would make an antibody to any integrin in the open conformation (whether it is chemically modified or naturally activated) other than an antibody directed to the specific open conformation mutations E284/E301C or K287C/K294C in the αL subunit I-domain and tested with the with the specific closed conformation mutation K289C/K294C in the αL subunit I-domain to indicate that the resultant antibody does not bind to the closed conformation. Without some kind of substantive structure of an I-domain in the open conformation, it would require undue experimentation for one of skill to make antibodies to that would bind to the open conformation but not to the closed conformation encompassed by the instant claims.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (modified I-domain in the open/closed conformations) to describe the claimed genus, nor does it provide a description of structural features that are common to species (I-domain). The specification provides no structural description of modified I-domain in open/closed conformations other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed modified I-domain looks like. The specification's disclosure is inadequate to describe the claimed genus of antibodies to I-domain in the open conformation but do not bind to the closed conformation.

It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence and the functional properties of the different parts of the protein. The specification does not teach which changes in the amino acid of αL other than E284/E301C or K287C/K294C would result in the open conformation. Therefore, the specification fails to provide sufficient guidance as to which specific substitutions of I-domains, other than αL I-domain, are essential for maintain an open or closed conformations and which changes can be made in the structure of an I-domain and still locked in the open/closed conformation.

Claim 76, recites an antibody comprises a portion of a human antibody and a portion of a non-human antibody. However, one of ordinary skill in the art would not know what portion is derive form a human and what portion derived form a non-human. Further, a combination of any human and non-human portions would not result in a functional antibody or an antibody that specifically binds to a modified integrin I-domain. For example, a framework region form a human and a framework form non-human for example would not result in a functional antibody. A constant domain from a human and a constant domain form non-human also would not result in a functional antibody. A combination of a framework (whether it is a human or non-human) and a constant domain (whether it is a human or non-human) would not result in a functional antibody.

Also, at issue is whether or not the claimed composition recited in claims 127-130 would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

Claims 117-124 recite that the antibody is linked to a therapeutic moiety. It appears that applicant is using the claimed antibodies for target delivery of a drug. However, in view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the antibodies as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed antibodies are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed antibodies with a reasonable expectation of success.

Consequently, without additional guidance in the specification, and the dearth of information in the art, for one of skill in the art to practice the invention as claimed, would require experimentation that is excessive and undue. The amount of guidance or direction needed to enable an invention is inversely related to the mount of knowledge in the state of the art as well as the predictability in the art (In re Fisher, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970)).

Applicant's arguments, filed 6/4/04, have been fully considered, but have not been found convincing.

Regarding the antibodies that bind "equally well" to both the open and closed conformation, Applicant declared that these antibodies are not antibodies that "specifically bind" to a n integrin

I-domain in the open conformation. Applicant submits that the disclosed monoclonal antibodies referred to by the Examiner are not examples of the claimed antibodies.

However, Applicant's argument attempts to limit the term "specifically bind" in a manner inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequences. That is an antibody "cross-reacts", i.e., binds to more than one protein sequence, does not mean that the antibody does not "specifically react" with both proteins.

For example, Bost et al. (Immunol. Invest. 1988; 17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies which bound either the HIV or IL-2 derived sequence did not cross-react with irrelevant peptides (e.g., "Results, page 579).

Consequently, it was well known in the art at the time the invention was made that antibody binding of distinct proteins was indeed specific. Therefore, an antibody that binds "equally well" to both the open and closed conformation of LFA-1 meets that claimed antibodies that "specifically bind to an integrin I-domain in the open conformation".

Applicant submits that the level of skill in art of antibody production was high at the time of filing, one skilled in the art would have been able to produce the claimed antibodies using a modified integrin I-domain as an antigen for immunization or as a target for screening a display library or otherwise in an known method.

The Examiner agreed with the applicant assertion that the level of the skill in the art of antibody production is high. However, the skill in the art needs to know what are those modifications in the I-domains of the integrin molecules that would result in an open conformation structure. Without some kind of substantive structure of an I-domain in the open conformation, it would require undue experimentation for one of skill to make antibodies to that would bind to the open conformation but not to the closed conformation encompassed by the instant claims.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 25, 27, 29-30, 73, 74, 76-80 and 107-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6, in view of U.S. Patent No. 5,843,712.

Huang *et al* teach five monoclonal antibodies BL5, F8.8, May.035, TS1/22 and TS2/6 which selectively bind to an integrin I-domain (see page 3163 under mAbs and Cell Lines, and page 3164 Figure 2 in particular). Those antibodies bind to specific epitope on the integrin αL subunit of I-domain of LFA-1 integrin (page 3164 Figure 2 in particular). Although Huang *et al* do not teach the specific antibodies bind to a modified I-domain of αL subunit containing amino acid substitutions E284C/E301C, wherein the modified integrin polypeptide is stabilized in the open conformation. These limitations are considered an inherent property of the reference antibodies. Huang et al further teaches that LFA-1 binds three cell surface ligands that are members of the Ig superfamily, intercellular adhesion molecule (ICAM)-1, ICAM-2, and ICAM-3 (see page 3162, introduction 1st ¶ in particular). Further, Huang et al teach that the antibodies in solution, (2μg of purified IgG or 2μlo of ascites) were added to 200μl (1% Triton X-100/150mM NaCl/20 mM Tris.HCl, pH 7.5) of the precleared supernatants (see page 3163, 2nd col., 2nd ¶ in particular).

As is evidenced by Lu *et al*, that antibodies against αL I domain of LFA-1, BL5, F8.8, May.035, TS1/22 and TS2/6 bind to the open or "active" mutants K287C/K294C of αL subunit of LFA-1 "modified I domain" (see Table 1 page 2394 in particular). Furthermore, Lu *et al* teach that BL5, F8.8, May.035, TS1/22 and TS2/6 antibodies strongly inhibited binding of both wild-type and mutant K287C/K294C of αL subunit of LFA-1 (page 2395, Table 2 in particular). Lu *et al* compare the binding of modified integrin I-domain in the open conformation (K287C/K294C) relative to the modified integrin I-domain in the closed conformation (L289C/K294C) as well as (see table 1 in particular) the wild type. The binding to the open and closed conformation mutants is almost equivalent among the antibodies or differs by only a few percentage points.

Further, as is evidenced by the specification on page 76, lines 7-8 and page 77, Table 6 that the affinity of E284C/E301C mutant is nearly comparable to K287C/K294C mutant affinity (e.g. predicted open conformation binds with high affinity).

The claimed invention differs from the reference teachings only by the recitation of a recombinant antibody, the antibody comprises a portion of human antibody and a portion of a non-human antibody in claim 76, a humanized antibody in claim 77, and a chimeric antibody in claim 78.

The `712 patent teaches that the expression of recombinant antibodies in mammalian cells offers great advantages with respect to post-translational modifications, stability, immunogenicity, and yields (see column 1, lines 40-45 in particular), whercin Sindbis virus vectors offer a powerful tool for the rapid production of genetically engineered antibodies (column 1m lines 1, lines 48-

56 in particular). The '712 patent further teaches that the Sindbis virus vector system can be useful to produce recombinant antibodies that replace immunoglobulin therapies that are presently being used in the treatment of certain inflammatory disorders, immunodeficiency states, and viral infections. The advantages of such recombinant antibodies (versus serum immunoglobulin therapy MAbs derived from mouse hybridoma cells) would be that they can easily be humanized. Further these antibodies can be custom designed to modify their specificity, and produced in very large quantities (see column 16, lines 8-16 in particular). Finally, the '712 patent teaches that the Sindbis virus vector system can easily be adapted to produce chimeric, humanized or human antibodies. The feasibility of producing high yields of humanized biologically active antibodies suggests that the Sindbis virus vector system can be useful for the generation of therapeutic antibodies. Results demonstrate that an antibody produced using the Sindbis virus vector system is able to protect mice against a lethal infection of the central nervous system (see column 15 lines 66-67 and column 16 lines 1-8 in particular).

Claim 80 is included because antibody is antibody irrespective of how it's made.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the antibodies taught by Huang *et al* recombinantly, chimeric, humanized or human taught by the '712 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the recombinant antibody offers great advantages with respect to post-translational modifications, stability, immunogenicity, and yields as taught by the '712 patent. Further, chimeric, humanized are human antibodies can be useful for the as therapeutic antibodies as taught by the '712 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 6/04/04 have been fully considered, but have not been found convincing.

12. Claims 25, 27, 29-30, 73, 74, 76-80 and 107-113 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6 in view of U.S. Patent No. 5,843,712 and further in view of Owens *et al* (1994).

The teachings of Huang *et al*, Lu *et al* cited as an evidentiary reference and the '712 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of an antigen binding fragment.

Owens *et al* teach the modification of murine antibodies such as a single chain antibody, a Fab fragment, or a $F(ab')_2$ fragment. Owens *et al* further teach antibody fragments are the reagents of choice for some clinical applications (see the entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the antibodies taught by Huang *et al* as Fab and $F(ab')_2$ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 127-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6 in view of U.S. Patent No. 5,843,712 as applied to claims 25-27, 29-30, 73-80 and 82 above, and further in view of U.S Patent No. 6,413,963.

The teachings of Huang *et al*, Lu *et al* cited as an evidentiary reference and the '712 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition and a pharmaceutically acceptable carrier in claims 127-130.

The '963 patent teaches pharmaceutical compositions prepared comprise a therapeutically effective amount of a compound (e.g. antibody) in a pharmaceutically acceptable carrier. The '963 patent further teaches that therapy with inhibitors of cell adhesion are indicated for any condition in which an excess of integrin-mediated cell adhesion is a contributing factor (see column 18, lines 28-41 and column 20 lines 11-12 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the antibodies taught by Huang *et al* reference in a pharmaceutical compositions in a pharmaceutically acceptable carrier taught by the `963 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because antibody pharmaceutical compositions are used in a therapy where any condition in which an excess of integrin-mediated cell adhesion is a contributing factor as taught by `963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 127-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6, in view of U.S. Patent No. 5,843,712 and further in view of Owens et al as applied to claims 25-27, 29-30, 73-80 and 82 above, and further in view of U.S Patent No. 6,413,963.

The teachings of Huang *et al,* Owens *et al*, Lu *et al* cited as an evidentiary reference and the `712 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of that the antigen binding fragment with a pharmaceutically acceptable carrier.

The `963 patent teaches pharmaceutical compositions prepared comprise a therapeutically effective amount of a compound (e.g. antibody) in a pharmaceutically acceptable carrier. The `963 patent further teaches that therapy with inhibitors of cell adhesion are indicated for any condition in which an excess of integrin-mediated cell adhesion is a contributing factor (see column 18, lines 28-41 and column 20 lines 11-12 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the antigen binding fragment taught by Huang *et al* in view of Owens et al in a pharmaceutical compositions comprising a pharmaceutically acceptable carrier taught by the `963 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because antibody pharmaceutical compositions are used in a therapy where any condition in which an excess of integrin-mediated cell adhesion is a contributing factor as taught by `963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. The following new grounds of rejections are necessitated by the amendment filed 6/4/04.

16. Claims 114-126 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 114 has no antecedent basis in base claims 30, 83, 75, and 103, because claims 30, 83, 75, and 103 recite a recombinant antibody/antibody or an antigen binding fragment thereof per se, whereas a conjugated antibody or fragment thereof is recited in claims 114.

B. The "physically linked detectable substance" recited in claims 115-116 has no antecedent basis in base claim 102. Base claim 102 only recites the "integrin I-domain is an I domain of αL".

C. Claims 117-121 have no antecedent basis in base claims 25, 30, 75, 83, and 103, respectively, because claims 25, 30, 75, 83, and 103 recite a recombinant antibody/antibody or an antigen binding fragment thereof per se, whereas a conjugated antibody or fragment thereof is recited in claims 25, 30, 75, 83, and 103.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 26, 75, 103 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc Natl Acad Sci 98:2393-2398, 2002).

Huang *et al* teach five antibodies BL5, F8.8, May.035, TS1/22 and TS2/6 which selectively bind to an integrin I-domain (see page 3163 under mAbs and Cell Lines, and page 3164 Figure 2 in particular). Those antibodies bind to specific epitope on the integrin αL subunit of I-domain of LFA-1 integrin (page 3164 Figure 2 in particular). Although Huang *et al* do not teach the

specific antibodies bind to a modified integrin I-domain in the open conformation, the antibodies bind to an activation specific epitope (I domain) on the integrin, the antibodies blocks an interaction between an integrins and a cognate ligand, wherein said modified I-domain of an αL subunit contains amino acid substitutions K287C/K294C or E284C/E301C and wherein modified LFA-1 I-domain contains amino acid substitutions K287C/K294C or E284C/E301C, all these limitations are considered an inherent property of the reference antibodies.

As is evidenced by Li *et al*, that antibodies against αL I domain of LFA-1, BL5, F8.8, May.035, TS1/22 and TS2/6 bind to the open or "active" mutants K287C/K294C of αL subunit of LFA-1 "modified I domain" (see Table 1 page 2394 in particular). Furthermore, Lu *et al* teach that BL5, F8.8, May.035, TS1/22 and TS2/6 antibodies strongly inhibited binding of both wild-type and mutant K287C/K294C of αL subunit of LFA-1 (page 2395, Table 2 in particular).

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to a modified integrin I –domain in the open conformation and binds an activation specific epitope on the integrin I-domain recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

19. Claims 114-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6, in view of U.S. Patent No. 6,572,856.

The teachings of Huang *et al*, , Lu *et al* cited as an evidentiary reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of that the antibody further comprising a physically linked detectable substance in claim 114, wherein the physically linked detectable substance comprises and enzyme, a fluorescenct material, or a radioactive material in claims 115-116, or the antibody further comprising a therapeutic moiety in claims 117-121, wherein the therapeutic moiety comprises a cytotoxin in claim 122, a chemical therapeutic agent in claim 124, a protein possessing a desired biological activity in claim 125, a toxin in claim 126.

The `856 patent teaches monoclonal antibodies immunospecific for C3b(i) are conjugated to a therapeutic moiety such as a chemotherapeutic cytotoxin, e.g., a cytostatic or cytocidal agent (e.g., paclitaxol, cytochalasin B or diphtheria toxin), a thrombotic or anti-angiogenic agent or a radioactive label. In another embodiment, monoclonal antibodies immunospecific for C3b(i) are conjugated to a detectable substrate such as, e.g., an enzyme, fluorescent marker, luminescent material, bioluminescent material, or radioactive material (see col. 8 lines 45 to col. 9, line 8 in

particular). Further, an antibody or fragment thereof can be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide. Therapeutic agents include antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), (e.g., vincristine and vinblastine). (see column 28, lines 15-38 in particular) the `856 patent teaches that the drug moiety can be a protein or polypeptide possessing a desired biological activity such as toxin (see col., 28, lines 51-55). The `856 patent further teaches that the anti-C3b(i) antibodies or fragments thereof are conjugated to a diagnostic or therapeutic agent can bed used diagnostically as a part of a clinical testing procedure to determine the efficacy of a given treatment regimen (see col., 27, lines 57-61 in particular). Finally, the `856 patent teaches that the antibodies specific for C3b(i) can be utilized to target tumor cells for the delivery of therapeutic or diagnostic agents, including cytotoxic, chemotherapeutic, immune-enhancing drugs, radioactive compounds, genetic material and immune effector cells (see col., 45, lines 1-5 in particular)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the antibodies and fragments thereof, which selectively bind to an integrin I-domain taught by Huang *et al* with a physically linked detectable substance, wherein the physically linked detectable substance comprises and enzyme, a fluorescenct material, or a radioactive material, or a therapeutic moiety, wherein the therapeutic moiety comprises a cytotoxin, a chemical therapeutic agent, a protein possessing a desired biological activity, a toxin taught by the `856 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such antibodies or fragments thereof which are conjugated to a diagnostic or therapeutic agent can bed used diagnostically as a part of a clinical testing procedure to determine the efficacy of a given treatment regimen. Further, such conjugated antibodies can be utilized to target tumor cells for the delivery of therapeutic or diagnostic agents, including cytotoxic, chemotherapeutic, immune-enhancing drugs, radioactive compounds, genetic material and immune effector cellsas taught by `963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. No claim is allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
July 9, 2004

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